

The Fern Reaction of Cervical Mucus

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Part I. The Effect of the Normal Ovarian Cycle and of Pregnancy

ABSTRACT

The fern reaction of endocervical mucus was tested in 100 non-pregnant and 200 pregnant women with a view to establishing the relationship of this fern pattern to normal ovarian cyclical changes and normal pregnancy. The fern appeared at day 7-9 of the cycle and disappeared at day 18-20. Twenty-eight of 100 pregnancies before 10 weeks yielded positive fern reactions; two of 100 pregnancies after 10 weeks yielded positive fern reactions. In the presence of a positive fern reaction, the administration of 10 mg. of norethynodrel (Enovid) daily for seven days led to prompt withdrawal bleeding in the absence of pregnancy. With a negative fern reaction, a spontaneous period ensues within 12 days in the absence of pregnancy. Two hundred women were tested for early pregnancy on this premise; in 198, a correct diagnosis was obtained.

SOMMAIRE

L'examen microscopique du mucus endocervical et la recherche de la réaction en feuille de fougère ont été effectués chez 100 femmes non gravides et chez 200 femmes gravides, en vue d'établir la relation existant entre la présence de cette image de fougère, les changements cycliques ovariens normaux et la grossesse normale d'autre part. L'image est apparue aux jours sept à neuf du cycle, pour disparaître aux jours 18 à 20. Chez 28 des 100 femmes enceintes, avant 10 semaines et chez deux autres après 10 semaines, la réaction de la feuille de fougère était positive. Quand la femme n'est pas enceinte, et en présence d'une réaction fougérienne positive, l'administration quotidienne d'une dose de 10 mg. de noréthynodrel (Enovid) pendant sept jours aboutit à un saignement de sevrage. Toujours en l'absence de grossesse, la réaction fougérienne étant négative, une période menstruelle spontanée s'ensuit dans les 12 jours. On a cherché à établir, par cette méthode, l'existence du début d'une grossesse chez 200 femmes. Le diagnostic s'est révélé correct dans 198 cas.

IN 1946 Papanicolaou¹ reported the presence of a palm-leaf or fern pattern on certain microscopic slides of dried cervical mucus. Rydberg² later demonstrated that this pattern was formed by salt crystals. Zondek³ subsequently pointed out that estrogen promotes sodium chloride excretion by the cervical glands and tends to enhance the fern reaction, while progesterone inhibits sodium chloride excretion and tends to prevent ferning. On this basis he suggested the use of the fern reaction slide test as a guide to evaluation of the state of estrogen-progesterone balance.

The following study was carried out to illustrate the effects of the normal ovarian cycle and of pregnancy upon the fern reaction.

METHOD

Samples of endocervical mucus were obtained with cotton-tipped applicators, spread on clean glass slides, and allowed to dry. The subjects so examined were divided into three series—A, B and C:

A. One hundred non-pregnant women who had normal periods occurring regularly every 26-30 days.

B. One hundred women with amenorrhea of 28-70 days' duration in whom subsequent pelvic examination confirmed the diagnosis of pregnancy.

C. One hundred women with amenorrhea of over 70 days' duration in whom pelvic examination had already confirmed the diagnosis of pregnancy.

Smears were examined microscopically at $\times 100$ magnification. Those with fern patterns measuring not less than 0.2 mm. (2 cm. under magnification) across the smallest diameters were classified as "fern positive"; those without such patterns were classified as "fern negative". Care was taken to exclude pseudo-fern patterns produced by the

TABLE I.—FERN REACTION DURING THE OVARIAN CYCLE AND PREGNANCY

	Fern positive	Fern negative
<i>Series A:</i>		
End of period—day 6	0	7
Day 7	3	1
Day 8	2	3
Day 9	6	2
Days 10-17	37	0
Day 18	2	1
Day 19	1	6
Day 20	2	3
Day 21—onset of period	0	24
<i>Series B:</i>		
Under 10 weeks' pregnant	28	72
<i>Series C:</i>		
10-20 weeks' pregnant	2	46
20-30 weeks' pregnant	0	39
Over 30 weeks' pregnant	0	13

alignment of cells rather than the crystallization of mucus. Slides were scanned in their entirety to avoid missing fern-positive areas.

RESULTS

Table I indicates that the fern reaction becomes positive at day 7-9 of the menstrual cycle and turns negative at day 18-20. Positive fern reactions were common in early pregnancy but rare after 10 weeks' gestation. No relationship to age or parity was detected.

DISCUSSION

The results of the examination of 100 women in Series A (Table I) are in rough agreement with those of Roland,² who found that the fern reaction appeared at day 5-7 and disappeared at day 20-22. These results may be interpreted as indicating that any woman who has ovulated and who has a negative fern reaction should menstruate within 10-12

days unless she is pregnant. This interpretation is essential to the devising of a test for pregnancy, described herein (Part II).

Ullery and Shabanah⁴ reported a positive fern reaction in 30% of pregnancies. Most fern reactions were found in early pregnancy and forewarned of an increased risk of abortion. Series B indicates a 28% incidence of positive fern reaction during the first 10 weeks of pregnancy, and Series C a 2% incidence of positive fern reactions in more advanced pregnancy. The disappearance of the fern pattern as pregnancy progresses is assumed to be due to increasing placental progesterone.

SUMMARY

Endocervical mucus from 300 women was examined for the fern reaction.

Findings during the normal ovarian cycle and during pregnancy are reported and discussed.

Part II. A Guide to the Early Diagnosis of Pregnancy

A CONSIDERATION of the findings reported in Part I gave rise to the following classification of short-term secondary amenorrhea in apparently healthy women:

A. Positive Fern Reaction:

1. Anovulation.
2. Delayed ovulation—probably having occurred less than five days previously.
3. Early pregnancy—in 25-30% of cases.

In anovulation or delayed ovulation the administration of a progestin should lead to prompt withdrawal bleeding, while in early pregnancy the administration of a progestin should not lead to withdrawal bleeding.

B. Negative Fern Reaction:

1. Delayed ovulation—probably having occurred more than five days previously.
2. Early pregnancy—in 70-75% of cases.

In delayed ovulation, menstruation should occur spontaneously within 12 days, while in early pregnancy no bleeding should occur.

The following study was carried out in an effort to demonstrate the accuracy of a pregnancy test based upon the above classification.

METHOD

Two hundred women with amenorrhea of 28-70 days' duration were tested for the fern reaction. Their ages ranged from 15-43 years, and their parity from 0 to 8.

If the fern reaction was positive, norethynodrel with ethynlestradiol 3-methyl ether (Enovid) was administered in a dosage of 10 mg. per day for

seven days. If withdrawal bleeding occurred within four days, the amenorrhea was considered to be due to ovarian dysfunction; otherwise it was considered to be due to pregnancy.

If the fern reaction was negative, no hormone was administered. If menstruation occurred within 12 days, the amenorrhea was considered to be dysfunctional; otherwise it was considered to be due to pregnancy.

RESULTS

In the two patients in whom pregnancy was diagnosed erroneously (Table II), withdrawal bleeding did occur, but not until the sixth and tenth days. The mistaken impression of pregnancy was harboured for two and six days, respectively.

TABLE II.—RESULTS OF FERN-REACTION PREGNANCY TEST

Positive fern reaction:	
Pregnancy diagnosed correctly.....	38
Pregnancy diagnosed erroneously.....	2
Pregnancy excluded correctly.....	40
Negative fern reaction:	
Pregnancy diagnosed correctly.....	97
Pregnancy excluded correctly.....	23

DISCUSSION

Correct results were obtained by this procedure in all but two of the patients so tested. It should be emphasized, however, that the test was not done if the period of amenorrhea exceeded 70 days, or if the patient showed clinical evidence of ovarian insufficiency. During the time when the 200 test patients were checked, smears were taken from several other women with periods of amenorrhea

ranging from 71 to 126 days. In five of these there was no clinical evidence of pregnancy; three showed positive fern reactions and all three had prompt withdrawal bleeding following the administration of norethynodrel (Enovid) (10 mg. per day for seven days). Two showed negative fern reactions and both had prompt withdrawal bleeding following the administration of the naturally occurring estrogen preparation, Premarin® (3.75 mg. per day for 14 days), and norethynodrel (10 mg. per day from the eighth to the fourteenth days of Premarin administration). In the same period three patients with clinical evidence of ovarian insufficiency were encountered; two of these complained of severe vasomotor flushes and breast regression, and one complained of continuing galactorrhea three months after nursing had been discontinued. All three showed negative fern reactions and had prompt withdrawal bleeding following the administration of conjugated estrogenic substances (Premarin) and norethynodrel with mestranol (Enovid) in the above dosages.

Of the 97 pregnancies associated with a negative fern reaction, 19 (20%) ended in abortion. Of the

38 pregnancies associated with a positive fern reaction, 12 (32%) ended in abortion. If patients who admitted that their pregnancies had been interfered with are excluded, the abortion rates become 9% and 26%, respectively. A later study is planned in which the usefulness of this test in predicting abortion will be studied in greater detail.

SUMMARY

A method for diagnosing early pregnancy, utilizing the fern reaction of cervical mucus, was devised and tested.

Pregnancy was diagnosed correctly by this procedure in 100% of patients and excluded correctly in 97%.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

BARÁNY AND THE CEREBELLUM

The next advance in our knowledge of the vesicular nerve was also made by Bárány in 1909. Just at this time he was greatly impressed with Ramon y Cajal's statement in his recently published work, "Histology of the Nervous System," that the branches of the vestibular nerve form an extraordinarily large number of connexions with the cerebellum. Combining this knowledge with Bolk's conclusions that in the cerebellar hemispheres of man is the controlling influence over the muscles of the extremities, and in the vermis the controlling influence over the trunk muscles, he set about to devise a method whereby, after irritation of the vestibular nerve, he should be able to examine the extremities. He soon found one suggested by the Graefe test used in diagnosing paralyzes of eye muscles, in which the method of examination is as follows: An object is placed before the patient's suspected eye (the other eye being kept closed) and he is directed to touch the object with his finger, first with the suspected eye open and then with it also closed. The normal invariably touches it correctly, but if there is paralysis present, there will be a deviation of the finger from the object. On this principle Bárány developed his *Zeigerversuch* or pointing reaction.

Now it is the function of the static labyrinth to acquaint us with our position in space and with changes in that position, and normally this fine mechanism is in perfect balance, but if a powerful impulse is produced in the semi-circular canals, mechanically by the caloric, turning, galvanic or fistula test, the central check is abolished, the balance upset, and the result of this loss of control is disturbed equilibrium in the eye muscles—nystagmus; and the muscles of the body and extremities—the reaction movements. If the strong impulse radiates from the central vestibular nuclei, in the floor of the fourth ventricle (medulla) to the vagus nuclei, we get nausea and vomiting.

Bárány's theoretical explanation of cerebellar localizations is that there exist in the cerebellar cortex certain definite centres which exert upon each particular joint or its con-

trolling group of muscles a pull or tonus in a definite and constant direction. Thus there must be at least four centres for controlling the movements of every joint, for example, an upward and downward, and an inward and outward movement for each shoulder joint, which would enable the normal individual to move the arm correctly in the vertical and horizontal planes without the aid of sight. Just as in the motor area of the cerebrum there are centres presiding over the voluntary movements of each small group, so with the cerebellum, there are separate centres for different joints, e.g., the shoulder, elbow, wrist, hip, knee, ankle, neck, etc. These various cerebellar centres normally act harmoniously and co-ordinate the movements of the various joints. Let us consider for a moment the right and left centre of the shoulder joint. These act like a pair of taut reins between which the arm moves, and by the tone or tension which it imparts to the muscles, the arm always moves exactly up or down in the same line and touches the finger correctly, i.e., there is normal pointing. But suppose the left rein is pulled more tightly than the right, then the arm must naturally deviate to the left and there is a pointing error to the left. We can produce a stronger pull on the left rein in the normal individual by syringing the left ear with cold water and then there will be a pointing error to the left as long as the nystagmus is to the right. This pointing error of both arms to the left can only come during a nystagmus to the right, by the innervation of the outward centre of the left arm in the left cerebellar hemisphere and the inward centre of the right arm in the right cerebellar hemisphere, so that both arms now deviate to the left. We also can produce the same pointing error to the left if we cut through or paralyze the right rein so that the left one only acts. Bárány's theory of cerebellar function seems to be well established, and his localizations have been recognized by no less a body than the German Neurological Society who at their annual meeting in Breslau in 1913, awarded him the Erb medal for his researches on the cerebellum.—D. H. Ballou, *Canad. Med. Ass. J.*, 4: 873, 1914.